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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,848	02/20/2004	Jef De Brabander	AP35699 090495.0282	7487

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EXAMINER	
OWENS, AMELIA A	
ART UNIT	PAPER NUMBER
1625	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/783,848	DE BRABANDER ET AL.	
	Examiner	Art Unit	
	Amelia A. Owens	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 10/27/2006

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6-12,14-17 and 23-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3,6-12,17 and 28* is/are allowed.

6)☒ Claim(s) *1,14-16 and 23* is/are rejected.

7)☒ Claim(s) *25-27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. §.119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1,3,6-12,14-17,23-28 are pending.

Claim Rejections - 35 USC § 102

2. Claims 1,23 remain rejected under 35 U.S.C. 102(b) as being anticipated by Northcote and West for the reasons of record.

Applicant's remarks and DeBrabander declaration have been considered but are not persuasive. Applicants are arguing that the references depict an 'inactive' stereoisomer of peloruside A. However, the references both attest to the antitumor activity of peloruside A. Thus, the references obviously tested the 'active' stereoisomer of peloruside A. Thus it follows that the authors of said references know or are able to determine the structure of peloruside A, making peloruside A available to the public before the present invention. The reference is available for what it teaches as a whole, and it clearly teaches peloruside A as an antitumor agent. Assuming applicants are correct and the references depict an incorrect structure, the references also teach how to isolate peloruside A from the marine sponge. Therefore, given the sponge of West or Northcote, the skilled artisan could extract peloruside A and determine a structure. The skilled artisan is aware of the various methods to isolate compounds from marine sponges. Thus, the skilled artisan would not have failed to prepare a composition of peloruside A.

See Hood, et al The novel cytotoxic sponge metabolite peloruside A, structurally similar to byrostatin-1, has unique bioactivity independent of protein kinase C, PMID: 11962513 (2001); Hood et al Peloruside A, a Novel Antimitotic Agent with Paclitaxel-like Microtuble-stablizing Activity, Cancer Research 62,3356-3360, June 15, 2002. The above references further support the examiner's position that peloruside A was known to the public as an antitumor agent. Applicants are not entitled to a patent just because they arguably depict the structure correctly of a known active compound. For claim 1, it is noted that applicants are claiming a composition. However, claiming an unpatentable compound in combination with a carrier does not render the combination patentable if it would be obvious in the prior art to utilize a carrier with the compound. It is well known in the pharmaceutical arts to use carriers to administer compounds.

For the above reasons, the rejection is applicable to all listed claims. Further, Northcote @ paragraph 24-26 and 55-57 teach the methods of claims 14-17,28.

Claims 14-17 are no longer included in the rejection as they no longer depend from claim 1.

Claim Rejections - 35 USC § 103

3. Claims 1,23,28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over West and Northcote for the reasons of record.

Applicants remarks and declaration have been considered but are not persuasive for the reasons given in above paragraph 2. Claims 14-17 are no longer included in the rejection as they no longer depend from claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 23, 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 23 formula 65G the designation overlaps the structure. Please correct.

In claim 24, step (a),(c),(d),(h), (i) lists compounds without commas or proper Markush ending.

5. Claims 25-27 are objected to under 37 CFR 1.75 as being a duplicate of claim 24. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP 7O6.03(k). Claim 24 is directed to method of producing peloruside A. Claims 25-27 merely state the product is peloruside A which is known from the generic claim 24.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In cases involving unpredictable factors, e.g., physical activity, the scope of enablement provided by the specification to one skilled in the art varies inversely with the degree of unpredictability of the factors involved. Cancer treatment, suppressing tumor growth, inhibiting growth of proliferating cells is known by the artisan to be highly unpredictable as underscored by Gura (Science, v278, 1997, pp. 1041-1 042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, lst column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Cancer treatment is known to be compound and disease specific, that is a particular compound or class of compound can be useful in treating a particular type or class of cancer.

Peloruside A has been tested via NCI cell line anticancer assay to determine its ability to suppress tumor growth, treat cancer, or inhibit growth of proliferating cells. The compounds tested are not commensurate in scope with the protection sought. Further, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening effects of potential drugs. However, clinical correlations are generally lacking. The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and the disclosed/claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a

"working example" if that example "correlates" with a disclosed or claimed method invention. The instant application contains no such animal model or example, therefore there is no correlation and the examples do not constitute "working examples."

Further, the greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri-dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vitro are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

Doses required to practice their invention are described@ page 24. There are no guidelines for determining the doses needed to provide a breast cancer effect *vs.* a CNS *system*

effect *vs.* a renal *system* effect. Are the identical doses to be used for treating these unrelated forms of cancer?

The artisan using Applicants invention would be a physician with a MD degree and several years of experience. Again, it is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). h) The scope of the claims involves all of the thousands of compounds of the claims as well as the hundred of diseases embraced by the term cancer. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." Based upon the relevant evidence as a whole, there is no reasonable correlation between the disclosed in vitro utility and an in vivo activity. In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

6. Claims 3,6-12,17,28 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amelia A. Owens whose telephone number is 571-272-0690. The examiner can normally be reached on Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas C. McKenzie can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amelia A. Owens
Primary Examiner
Art Unit 1625